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08/469,492

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/469,492	06/06/95	WEINER H	1010/16959-U

HM11/0218

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EXAMINER	
DUFFY, P	
ART UNIT	PAPER NUMBER
1645	13

DATE MAILED: 02/18/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 12-25-97.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 37-39, 42-49, 52-57 and 59-65. is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) ~~37-39~~, 42-49, 52-57 and 59-65. is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

★ U.S. GPO: 1996-409-290/40029

Response to Amendment

1. Effective February 7, 1998, the Group and/or Art Unit of U.S. Patent application S.N. 08/469,492 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Technology Center 1600, Group 1640, Art Unit 1645.

2. The amendment filed November 27, 1997 has been entered into the record.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

4. Any rejections or objections not specifically reiterated herein are withdrawn.

5. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 11-25-97 has been entered.

Rejections Maintained

6. The rejection of claims 37-39, 42-49, 52-57 and new claims 59-65 under 35 U.S.C. 112, first paragraph is maintained for reasons made of record for claims 37-58 in Paper No. 6, mailed 12-31-96.

Applicants assert that the examiner has failed to give proper weight to the evidence submitted with the Amendment mailed March 31, 1977 with respect to whether a person of skill in the art would have been able to make and use the invention in view of the guidance in the specification and general knowledge in the art. Applicants indicate that an enablement rejection

based on grounds of cross-species administration is improper and should be withdrawn because the Patent Office is not the FDA. This is not persuasive because the specification under 35 U.S.C. 112, first paragraph must teach how to make and use, the instantly claimed subject matter. The specification does not teach how to use cross-species proteins. Applicants also assert that the examiners conclusions with respect to the correlation of the EAE and NOD mouse with human disease are unfounded and provides a declaration by Dr. Malcolm Fletcher that the results from the trials relied upon by the examiner do in fact show a therapeutic effect. Dr. Malcolm Fletcher attests that the data are encouraging rather than ineffective as the examiner asserts because it reduces the attack rate as indicated by Exhibit I. Dr. Fletcher attests that the apparent lack of results for "Mayoral" (i.e. myelin basic protein) is due to the lack of side effects of the drug and a strong placebo effect. This is not persuasive because the function of a "control" such as a placebo is to rule out effects due to controls. In Exhibit I, clearly the placebo works better than the drug, thus the skilled artisan can not rule out that the effect of the drug on autoimmune disease was "placebo". The data support the examiners position that the placebo was better than the drug itself and thus is ineffective. Dr. Fletcher also discusses the concomitant β-interferon use and conclude that the combination was better than the placebo in reducing attacks and attributes this to the Mayoral. This is not persuasive because a proper interpretation of the results from a combination of drugs must provide individual controls. The skilled artisan could not reasonably conclude that the effect of the β-interferon and Mayoral is the result of either drug in the absence of controls demonstrating the effect of either alone. Applicants arguments drawn to the combination of β-interferon and Mayoral are not effective because this is not commensurate in scope with the claims which are drawn to the administration of a single reagent. The results submitted do not support applicants position, the treatment was

no better than placebo. If a drug is not better than the placebo it is not effective. The Exhibits I and II are therefore not persuasive and the art does not reflect the correlation of the outcome in animal model with the human disease. The evidence provided by applicants is seen to support that examiners position that the EAE mouse is not reasonably predictive the human response. Applicants indicate that the rejections are improperly based on a lack of utility and no utility rejection has been made and thus a rejection under 112, first paragraph is improper and the examiner has not presented a prima facie case. These comments are noted but applicants are reminded that the statute under 112, first paragraph the specification must teach how to make and use and the art teaches that myelin basic protein is not effective. The specification fails to teach how to use, for all the reasons previously set forth. Applicants also provide a declaration of Dr. George S. Eisenbarth in regard to the NOD mouse as a model for type I diabetes. The evidence with the NOD mouse is noted however, glutamic acid decarboxylase GAD) is an autoantigen in this model (Cohen et al "Autoimmune Disease Models, A Guidebook, Academic Press, 1994 page 154) and thus does not meet the claim limitations. This declaration references rejections applied not in the instant application. The declaration references many papers not provided by applicants and thus can not be properly evaluated. The declaration supports the position of the examiner because it states on page 5, .."insulin orally administered to patients with overt Type I diabetes can have little tolerizing effect because these patients have few, if any, beta cells remaining and with time present no signs of autoimmune inflammation." Thus, it appears in view of the declaration that tolerization treatment of overt diabetes is predicted to fail and supports the examiners position that one of skill in the art would have reason to doubt that administration after overt disease in the ongoing immune response will have a predictable and reproducible effect. Moreover, the teachings of the specification are limited to insulinitis and not

overt diabetes. Since insulinitis occurs before the onset of diabetes *per se*, it is not apparent that administering an agent after the insulinitis stage will be effective for treating diabetes, a position which is amply supported by the declaration of Dr. Eisenbarth. Applicants also provide evidence demonstrating that evidence of bystander suppression in other animal models. This is not persuasive because applicants fail to link the animal models with effective human responses and these animal models are not provided for in the specification and do not test glucagon. Applicants assert that the examiner has not provided evidence that the administration of GAD would not treat an autoimmune disease in humans or mouse after the onset of autoimmunity. The examiner does not have to provide facts to support the position but must merely provide a scientific basis or reasoning. In the instant case, suppressing an ongoing autoimmune response is well known to be difficult in the art because once the process is started and cells proliferate, make memory cells it is difficult to suppress or divert the ongoing robust immune response. Applicants have provided no evidence that demonstrates that the ongoing immune response can be diverted. Applicants provide articles published in 1996 that show bystander suppression is in fact an effective mechanisms for suppressing an immune response. The first article, Von Herrath et al address antigens specifically excluded by the claims and the specific mouse model used was not in the prior art at the time the invention was made. Applicants submit that in view of the Von Heareth et al article, the examiner would not have reason to doubt that one could effectively divert an on going immune response. This is not persuasive because the two animal models use different modes of administration of different antigens and thus can not be properly compared. Therapeutic dosage determination is not routine in autoimmune disease is not predictable because, as with myelin basic protein, the animal models are not reasonably predictive of human responses. In autoimmune diseases and bystander antigens, since the

models are not reasonably predictive of human response, contributions as determining dosages are not routine in the art and require independent thought and experimentation, such contributions are not minor details. Finally, the while the courts have held that:

> "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research." (Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001).

The specification fails to provide an effective dose of any bystander antigen within the scope of the claims. The specification is not enabled and the rejection is maintained.

7. The rejection of claims 48-49, 52-55, and new claims 56, 62, 63, and 64 under 35 U.S.C. 102(b) as being anticipated by the Merck Manual is maintained for reasons made of record for claims 48-50 and 52-55 in Paper No. 6, mailed 12-31-96.

Applicant assert that the now recited "and wherein said dosage form is adapted for nasal or mouth administration" removes the art of record. This is not persuasive because it is not clear how "adaptation" removes the art since suspension in saline of the invention would properly adapt the dosage form for administration by nebulizer for inhalation or orally. Thus, the suspension of the agent in saline inherently functions to "adapt" the composition when the composition is administered as a saline, aerosol or dry powder form. The rejection is maintained because it is unclear how the dosage form is adapted if not suspended in a pharmaceutically acceptable carrier.

8. The provisional rejection of claims 37-39, 42-49, 52-57 and 59-65 as previously applied to claims 37-58 as being obvious over 08/472,017 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed.

9. The provisional rejection of claims 37-45, 47-55, and 57 and new claims 59-65 as previously applied to claims 37-45, 47-55, and 57 as being obvious over 08/461,591 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed.

10. The provisional rejection of claims 37-39, 42-49, 52-57 and new claims 59-65 as previously applied to claims 37-58 as being obvious over 08/461,662 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed.

11. The provisional rejection of 37-39, 42-48, 52-57 and new claims 59-65 as previously applied to claims 37-46 and 48-58 as being obvious over 08/468,996 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed.

New Rejections

12. Claims 37-39, 42-49, 52-57 and 59-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Upon review of the prosecution history of the instant application the following is noted. The initial application provided for inhalable forms of bystander antigens which was amended by preliminary amendment on June 6, 1995 (Paper No. 5) to nasal administration by applicants pointing to page 23, lines 29-32. This passage does not support nasal administration. This passage specifically teaches away from the concept of nasal administration of any of the bystander antigens of the specification. Nasal is not equivalent to inhalable. Thus, the amendment of the claims to include nasal rather than "inhalable" is deemed to constitute new

matter to the claims and to the specification because it introduces new concepts which are specifically taught away from in the specification.

As to claims 48 and every claim dependent thereon, applicants have now amended the claims to recite "adapted for nasal or oral administration". The specification fails to teach by way of written description how "adapted for nasal or oral administration" further defines the pharmaceutical drug composition. Applicants have failed to point to written descriptive support for the amended claim language, such that a clear concept of "adaptation" can be ascertained. Applicants are requested to point to the specification by page and line number where written descriptive support for the amendment can be found.

13. Claims 60, 61, 63, 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to the claims, the recitation of "substantially" renders the claims indefinite because there is no definition in the art or in the specification, of what encompasses "substantially" in regard to purity or free from autoantigens. Thus, the metes and bound of the claims can not be ascertained.

Status of Claims

14. All claims stand rejected.

15. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310.

Patricia A. Duffy, Ph.D.
February 17, 1998

Patricia A. Duffy, Ph.D.
Patent Examiner
Group 1640